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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,788	03/22/2004	Steven C. Quay	03-04US	9945

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EXAMINER	
HEARD, THOMAS SWEENEY	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
03/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/805,788	QUAY ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,12,16 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *3-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 12, 16, 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Applicants Amendments to the claims received on 1/29/2008 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 10/29/2007 are hereby withdrawn.

Claim(s) 3-8, 12, 16, 20-28 are pending. Applicants have added claim(s) 20-28. Claims 3-7 remain withdrawn. Applicants have cancelled claims 9-11, 13-15, and 17-19. Claims 8, 12, and 16, and the new claims 20-28 are hereby examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 8, 12, 16, and the new claims 20-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour Pharmeceutical Company (EP 0115627) referred to as APC, and Moise Azria et al U.S. Patent 5,759,565, both from Applicant's IDS and made of record in th previous office action, and Grebow et al US Patent 5,026,825.

In instantly claimed invention is drawn to a composition comprising: an aqueous solution of calcitonin salmon at a concentration of 2200 International Units (I.U.) per ml or 0.0355% w/w; Chlorobutanol at a concentration of about 0.25% weight/weight; sodium chloride at a concentration of 0.85% weight/weight; and hydrochloric acid in an amount sufficient to adjust the pH of the solution to 3.5; wherein the composition is suitable for intranasal administration in humans.

Azria et al teaches calcitonin in a saline solution (tonicity) of 0.75 % w/w which is about 0.85% at a pH of 3 to 5 where the pH has been adjusted with HCl. The amount of calcitonin used in the invention is taught to be between 150 and 8,000 MRC units (I.U. of Activity) of salmon calcitonin, readable on Applicants 2200 I.U. per ml. The composition is taught to be to be stored under an inert Nitrogen atmosphere for stability of the calcitonin. Chlorbutanol is also taught as being use in the nasal composition but suffers from some drawbacks when used at 0.6%. Azria et al does not teach the use of

Chlorbutanol at ranges lower than that of 0.6%, see, Column 4 and lines 6-20; column 6 and lines 11-18; and column 7 and lines 32-37.

APC teaches pharmaceutical composition for nasal administration comprising calcitonin at a concentration range of 1 to 150 ug/ml where the concentration and dosage levels of calcitonin are with a potency of about 4000 I.U. per mg, well within the range taught by Azria et al and instantly claimed. APC teaches the use of a Tonicity Adjuster in the range of 0.01-.5 %w/v readable upon the saline solution of Azria et al. APC also teaches the use of Chlorobutanol (a preservative) in the range of 0.001-2.0 % w/v which is instantly claimed, see page 5 and line 5-18 and page 6 for the additive ranges.

Grebow et al, US Patent 5,026,825 teaches an intranasal composition comprising from about 0.0001% W/V to about 15% W/V of a polypeptide salmon calcitonin or having calcitonin activity (potency of from about 100 to about 10,000 international units per mg of polypeptide readable upon Applicant 0.355% w/w of Claim 8 and 2200 I.U of Claim 12 and 16, see Claims 1-7 of '825. Grebow further teaches the preservative Chlorobutanol in ranges from 0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v. Note that the examiner is taking the mass of water to be 1 g/ml therefore which makes the translation fro w/v% to be essentially identical to that of w/w%.

It would have been obvious at the time of the instantly claimed invention to optimize the concentration of Chlorobutanol %w/v for any deleterious effects as the art clearly teaches the use of Chlorobutanol in combination with calcitonin and at

concentrations as low as 0.1% w/v as taught by Grebow et al. It would have been obvious to one skilled in the art at the time of invention to determine all operable and optimum components in the claimed composition of U.S. Patent No. Armour Pharmeceutical Company (EP 0115627) and Moise Azria et al U.S. Patent 5,759,565, because the component % w/v are an art-recognized result-effective variable that is routinely determined and optimized in the composition arts. One would have been motivated to modify the composition as taught by both APC, Azria et al, and Grewbow to optimize the concentration parameters to eliminate undesirable effect of any given component and or enhance the effect of a given component as calcitonin, saline, Chlorobutanol, as the art teaches both their combination and use, and within the ranges instantly claimed. Given the intended use of the composition is for nasal administration, putting the composition into a sprayer is obvious on its face, readable upon Claims 20-28. The parameters of the actuator tip, spray pattern, droplet size etc... are also art-recognized result-effective variables that are routinely determined and optimized for nasal administration in the composition arts. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicants' arguments have been carefully considered but are not found persuasive. Applicant have argued:

(I) In the previous response, Applicant submitted that Azria et al. purposefully and intentionally teach away from use of chlorobutanol in a calcitonin solution by

showing specific and credible evidence that chlorobutanol does not sufficiently destroy microorganisms in a calcitonin solution. Further, Applicant submitted that the APC reference (EP '627) is not pertinent because it provided no specific factual evidence on which a person of ordinary skill in the art could have relied in 1998 when the unsuitability of chlorobutanol was shown in fact by Azria et al. Thus, Applicant submitted that a person of ordinary skill in the art in 1998, in view of Azria et al., would have been strongly dissuaded from using chlorobutanol in a calcitonin nasal spray, and would have been led to use the working alternative benzalkonium chloride which Azria et al. showed was operable. This is a clear teaching away from selecting chlorobutanol as a preservative in a calcitonin solution. Azria et al. expressly disparaged the use of chlorobutanol and successfully demonstrated the use of an alternative.

(II) In the office Action mailed October 29, 2007, Examiner turned to the newly cited reference Grebow et al. U.S. Patent 5,026,825 for its disclosure of chlorobutanol in a calcitonin formulation at a concentration of 0.1%(w/v), which Examiner stated is "lower than that of the Applicants." The Examiner concluded that Grebow et al. somehow provided new evidence of the suitability of chlorobutanol in a calcitonin formulation.

(III) Applicant respectfully submits that Grebow et al. adds no new information whatsoever to the discussion and does not obviate the teaching away expressly recited in Azria et al. Grebow et al. discloses "preservatives" at column 11, line 50, and provides a list of eight or more possible preservatives including chlorobutanol at column 12, lines 1-16. Lastly, Grebow et al. discloses numerous prophetic formulations of calcictonin, one of which recites chlorobutanol at 0. l%(w/v) (column 13, line 14). But no working examples in Grebow et al. show the use of chlorobutanol. The information disclosed in Grebow et al. does not go beyond that found in the APC reference which was discussed in Applicant's previous response. To wit, the APC reference also discloses a prophetic formulation of calcitonin with chlorobutanol at 0.1%(w/v) (page 10).

(IV) Moreover, the information disclosed in Grebow et al. does not reduce the force of the teaching away expressly described in Azria et al. Importantly, both Grebow et al. and the APC reference were published long before Azria et al. Because Azria et al. provided specific and credible test results showing that chlorobutanol does not sufficiently destroy microorganisms in a calcitonin solution, this fact would have been reasonably relied upon by a person of ordinary skill in the art. Neither Grebow et al. nor the APC reference provide any information that would cast doubt on the laboratory test results of Azria et al. Thus, a person of ordinary skill in the art in 1998 or later, in full view of the published results of Azria et al., would have been strongly dissuaded from using chlorobutanol in a calcitonin nasal spray, and would have been steered to the operable alternative benzalkonium chloride. In sum, the prophetic disclosures of Grebow et al. and the APC reference are far outweighed by the specific and credible factual evidence of Azria et al. that chlorobutanol does not sufficiently destroy microorganisms in a calcitonin solution. Further, in light of the Declaration of Henry R. Costantino submitted previously by Applicant, which states that chlorobutanol was

found to be acceptable as an antimicrobial in a calcitonin composition, and which further states that in view of Azria et al. there would have been no reasonable expectation of success of using chlorobutanol in a calcitonin nasal pharmaceutical composition, it is clear that Applicant's discovery that formulations of calcitonin salmon containing chlorobutanol have acceptable antimicrobial effect shows that claims 8, 12, and 16 are patentable over the cited references, either alone or in any combination.

Regarding the teaching away from Applicant's arguments in (I) above, this is not found persuasive. Azria et al teaches that Chlorbutanol suffers from some drawbacks when used at 0.6%. This indicates that use at this concentration or above suffers some drawback, not at concentrations below. Thus the teaching away is at 0.6% or higher. It is not a teaching away from using Chlorobutanol below those concentrations. Grebow et al clearly showed Calcitonin and Chlorobutanol together and at lower Chlorobutanol concentrations than taught by Azria et al. The Arguments of (II) and (III) are not found to be persuasive. First, Chlorobutanol is taught at the lower concentrations that Azria found to be less desirable, and that specific example is given in Table on Column 13. The Examiner does not find it to be prophetic, as Grebow et al is giving a specific formulation to make and use. There is no picking and choosing from a list of Markush of ingredients, but rather a specific formulation calling for Chlorobutanol and Calcitonin together in a container, and the Chlorobutanol is far below the concentration found to have a deleterious effect on a rubber stopper of Azria et al. Regarding the arguments in (IV), that the Applicants found antimicrobial activity at 0.1%, if antimicrobial activity was found by Applicants at the concentration, it would have also been found with Grebow et al, and the antibiotic activity would have had to have been present in the composition. One cannot conceive of a composition where Calcitonin and Chlorobutanol are made

identically in two separate labs, and the concentration of Chlorobutanol is 0.1% in both compositions, yet the antimicrobial activity is observed in one lab but not the other. Given that fact that the Chlorobutanol is the compound that provides the antimicrobial activity or property. Applicants have not overcome the rejection and the arguments for the teaching away of Chlorobutanol at concentration less that 0.6% is not persuasive over a specific example (Example 10) and ranges taught by Grebow et al and the combinations of the references supra. Therefore, the rejection stands.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m.. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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